IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Terri L. Butler et al.	Examiner:	Traviss C. McIntosh, III
Serial Number:	10/692,338	Group art unit:	1623
Filed:	23 October 2003	Docket:	BP.028US2
Title:	COMPOSITIONS AND METHODS FOR IMPROVING CARDIOVASCULAR FUNCTION		

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA, 22313-1450

I, John A. St. Cyr, hereby declare as follows:

1. I am a joint inventor of the above referenced invention. I have received the following degrees from the University of Minnesota: BA, 1973; BS, 1975; MS, 1977; MD, 1980; Ph.D., 1988. In addition, I completed a residency in General Surgery at the University of Minnesota in 1988 and a residency in Cardiovascular Surgery at the University of Colorado in 1991. Since 1991, I have been an independent consultant in research for various companies, investigating cardiovascular methods and devices, including energy metabolism. Since 1995, I have consulted with Bioenergy, Inc., the assignee of this patent application, where I am Medical Director and a minority shareholder.

During the period of my Ph.D. studies, I began working in the laboratory of Dr. John E. Foker, investigating potential adenine nucleotide improvement following myocardial ischemia. Some of the findings are included in the Foker Patent (4,719,201). I have published over 100 scientific papers and abstracts, about 30 of which relate to ATP metabolism. Two of these papers are of record in this case.

2. In the Office Action of June 16, 2006, Examiner McIntosh has rejected pending

claims 1-3 and 6 on the grounds of obviousness over U.S. Patent 6,218,366. I respectfully disagree and herein explain why the present invention is not obvious from the prior art.

3. Ribose is a well-known, natural carbohydrate, with an established role in energy metabolism. Many studies have been performed over the last forty years demonstrating that ribose increases cellular ATP in hearts and skeletal muscle. Some of these experiments on isolated tissue do not approximate a whole body effect because they are limited in time and are not in circuit with other body organs that affect ribose metabolism (e.g., kidneys and liver.) Some whole animal acute (hours) studies have shown positive similar results with ribose.

4. The earliest whole body with long term survival studies that we were aware of at the time this application was filed were those of Dr. John Foker and Dr. John St. Cyr. Intravenous ribose showed a remarkable ATP recovery in dogs subjected to global ischemia, during which myocardial ATP levels were lowered to about 50% of baseline. The ribose was given intravenously, with 100% bioavailability, at about 17 grams per day to a 25 kilogram dog.

5. Dr. Wolfgang Pliml carried out several studies to see the effect of oral ribose in various populations, including patients with stable coronary artery disease (reference of record in this case). His dosage was 15 to 20 grams and he never continued the study past three days of administration. From my own experience, I know that the bioavailability of high doses of ribose is not 100% and that unabsorbed ribose is metabolized and excreted, which may cause gastrointestinal problems We believe that the short duration of Dr. Pliml's studies was due to the gastrointestinal effects seen, which may have precluded patient compliance.

6. We first thought to investigate whether ribose would have a beneficial effect for persons not subjected to ischemic shock, that is, "healthy" persons. It was predictable that "healthy" persons were already at daily maximal ATP production/turnover. Dr. Foker's and Dr. Pliml's work taught that high doses were necessary for a beneficial effect, but high doses may not be sustainable. We experimented with lower single doses and found that ten grams of ribose were tolerated by only a few subjects; eight grams of ribose were tolerated by most subjects and five grams of ribose were tolerated by nearly all subjects. Looking at the other side

of the equation, we found that a one-gram dosage was not effective, two grams somewhat effective and five grams effective for most subjects. Based on these preliminary dosing results, the further trials described in U.S. Patent 6,159,942, issued December 12, 2000, were carried out.

7. Having shown that "healthy" persons could increase their tissues energy status with low doses of ribose, we investigated whether the tolerable, low doses were sufficient to benefit congestive heart failure (CHF) patients. The expectation was that CHF patients would require doses on the order of those given by Dr. Pliml to his coronary artery disease patients in order to show a beneficial effect. Also unknown was whether any benefit was transient or sustainable. The study of Dr. Omran and myself confirmed that the lower total daily doses disclosed in the present application were effective, tolerable and sustainable.

8. Having established the preferred regimen, we experimented with various substrate or supplement combinations to ribose. An early composition added a vasodilator, arginine, to ribose, which increased the ribose effect, presumably by vasodilation. We discontinued this product because the product was less stable, arginine being delisquescent, and also had a bitter taste. More importantly for CHF patients, many are already using a vasodilator. Likewise, the other vitamins and cofactors listed in the application were eliminated, as it was believed that patients could more economically take these supplements separately. Two added supplements (which are different from the initial formula) are currently offered: magnesium and malate in one of the two ribose products. These have been found to be of added benefit to certain patients, including those with fibromyalgia.

9. Ribose products as a medical food, recommended for CHF patients were introduced in 2004. The products are supplied in two ways, either through physicians/clinics or direct from Bioenergy following recommendation by a physician. Now, only two years later, sales have increased to a level of about $500,000 per month, with about 10,000 patients currently taking one of the two products, many of them for more than two years.

10. In conclusion, although ribose might have been suspected to be of use in managing CHF, in the forty years since the first studies and the twenty years since Dr. Foker's dog studies, no other entity has succeeded in entering this lucrative market by discovering the regimen that is effective, tolerable and sustainable.

11. I hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issue thereon.

By: _____ Date:_____

John A. St. Cyr, M.D., Ph.D.

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STATEMENT UNDER U.S.C. §103 (c)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA, 22313-1450

I, Bruce C. Faulken, hereby declare as follows:

1. I am General Counsel for Bioenergy, Inc., the assignee of the above referenced Patent Application.

2. Dr. Terri Butler and Clarence Johnson were employees of Bioenergy and subject to a duty to assign at the time the inventions were made. Dr. John St. Cyr, Dr. Steven Sawada and Dr. Dean MacCarter and were subject to a contractual duty to assign at the time the inventions were made.

3. Since all of the inventors of the above referenced Patent Application and U.S. Patent No. 6, 218, 366 were under a duty at the time the inventions were made to assign the inventions disclosed in the respective applications to Bioenergy, Inc..and did so assign the applications, the subject matter and claimed inventions were commonly owned at the relevant time.

Bruce C. Faulken 11/14/06

Bruce C. Faulken Date
General Counsel
Bioenergy, Inc.